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(54) Title: HIGH-PRECISION MEASURING METHOD AND APPARATUS PARTICULARLY USEFUL FOR NON-INVASIVELY MONITORING GLUCOSE LEVELS

(57) Abstract: A method and apparatus for monitoring a condition having a known relation to, or influence on, the transit time of a cyclically-repeating energy wave moving through a transmission channel, by: (a) transmitting a cyclically-repeating energy wave through the transmission channel from a transmitter at one end to a receiver at the opposite end; (b) continuously changing the frequency of the transmitter according to changes in the monitored condition while maintaining the number of waves in the transmission channel as a whole integer; and (c) utilizing the changes in frequency of the transmitter to provide a continuous indication of the monitored condition. Operation (b) is preferably performed by detecting a predetermined fiducial point in each cyclically-repeating energy wave received by the receiver, but may also be performed by the use of a phase-locked loop circuit, to maintain the number of energy waves in the loop of the transmission channel as a whole integer.

HIGH–PRECISION MEASURING METHOD AND APPARATUS PARTICULARLY USEFUL FOR NON–INVASIVELY MONITORING GLUCOSE LEVELS

RELATED APPLICATIONS

The present application is related to International Applications PCT/IL00/00241, Publication No. WO 00/67013, and PCT/IL02/00854, Publication No. WO 03/035321, corresponding to US Patents 6,621,278 and 6,856,141; it also includes subject matter of US Patent Application 10/844,398 filed May 13, 2004, and Israel Patent Application 166,760 filed February 8, 2005, the priority dates of which are hereby claimed.

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates broadly to high precision measuring methods and apparatus, and particularly to methods and apparatus for measuring various parameters or conditions having a known relation to, or influence on, the transit time of movement of an energy wave through a medium.

The present invention also relates to a method and apparatus for non–invasively monitoring the concentration of a target substance in a body. This aspect of the invention is particularly useful for measuring the concentration, or changes in the concentration, of glucose within the blood of a person, and is therefore described below with respect to that application, but it will be appreciated that the invention could advantageously be used in many other applications.

As brought out in U.S. Patent 6,621,278, many measuring techniques are known for measuring distance, temperature, and other parameters, but such known techniques generally increase in expense according to the precision desired, and also generally have an upper limit as to the precision practically attainable by the technique. For example, the measurement of distances of meters or kilometers with a precision of microns or fractions of a micron is extremely expensive, if attainable at all. The same limitations apply with respect to measuring temperature, force, and other conditions.

Frequent monitoring of blood glucose level is critical for those suffering from diabetes. Currently, glucose measurements are generally performed by the individual, by pricking a fingertip and applying a drop of blood to a test strip composed of chemicals

sensitive to the glucose in the blood sample. However, this method is very painful and usually inconvenient, particularly when done many times (e.g., 4–7 times) per day as recommended.

It is presently estimated that over 18 million people in the USA suffer from diabetes, and that this number will dramatically increase, to about 24 million in 2010. Considerable research and development has been conducted along many different avenues in an attempt to develop an effective non–invasive glucose monitoring device, as shown by the many technical articles that have been published on this subject and the many patents that have issued. Nevertheless, despite this dramatically increasing need for a method for monitoring blood glucose levels in a non–invasive, painless and convenient manner, and despite the considerable research and development efforts that have been devoted to developing such a device, no such device is yet commercially available, insofar as we are aware, having the accuracy, reliability and repeatability needed for general use.

While this problem is particularly acute with respect to monitoring blood glucose levels, the problem is also present in monitoring the concentration of other constituents of blood, such as cholesterol, or the constituents of urine, or of other biological fluids, industrial fluids, other bodies, etc.

BRIEF SUMMARY OF THE PRESENT INVENTION

The above–cited US Patent 6,621,278 discloses a method of monitoring a condition having a know relation to, or influence on, the transit time of a cyclically–repeating energy wave moving through a transmission channel from a transmitter at one end to a receiver at the opposite end, comprising the following operations:
(a) transmitting a cyclically–repeating energy wave through the transmission channel;
(b) continuously changing the frequency of the transmission according to changes in the monitored condition while maintaining the number of waves in a loop including the transmission channel as a whole integer; and (c) utilizing the changes in frequency of the transmission to provide a continuous indication of the monitored condition.

According to one aspect of the present invention, there is provided a method as set forth above, characterized in that operation (b) is performed by a phase–locked loop circuit having an input from said receiver, and an output controlling said transmitter.

According to another aspect of the invention, there is provided a method as set forth above, characterized in that the frequency of the transmitter is continuously controlled by: connecting a voltage–controlled oscillator to drive said transmitter and also to provide a first input to a phase detector; utilizing the output of said receiver to provide a second input to said phase detector and to produce an output from said phase detector corresponding to the difference in phase between the first and second inputs; and utilizing said output of the phase detector to control the voltage–controlled oscillator to drive said transmitter such that the number of waves in the loop including said transmission channel is a whole integer.

The cyclically–repeating energy wave may be an electromagnetic wave, an acoustic wave, or an acoustic wave generated according to the "photoacoustic effect", i.e., by the impingement of an electromagnetic beam against a target. In a preferred embodiment of the invention described below, the electromagnetic beam is a laser beam which generates a photoacoustic wave for non–invasively monitoring the level of glucose in blood.

According to a further aspect of the present invention, there is provided a method of non–invasively measuring the concentration, or change in concentration, of a target substance within a body, comprising the operations: activating a pulse source to apply to the body a series of pulses of energy highly absorbable by the target substance, as compared to other substances, to heat the body and to generate therein, by the photoacoustic effect, a series of acoustic waves propagated through an acoustic channel in the body at a frequency corresponding to that at which the energy pulses are applied to the body; detecting the acoustic waves to produce an electrical signal having a frequency corresponding to the frequency of the acoustic waves generated by the photoacoustic effect, and thereby to the frequency at which the energy pulses are applied to the body; controlling the pulse source to change the frequency at which the energy pulses are applied to the body, and thereby the frequency of the acoustic waves, such that the detector detects a whole integer number of wavelengths in the acoustic channel irrespective of variations in the target substance concentration within the body; and utilizing a measurement of the frequency, or change in frequency, of the pulses to produce a measurement of the concentration, or change in concentration, of the target substance.

The "photoacoustic effect" utilized in the above method is well known and has long been used for non–invasively producing various types of measurements, e.g. temperature, pressure, composition, etc. It has also been proposed for use in non–invasively monitoring blood glucose levels, as described for example in US Patents 5,348,002, 5,348,003, 5,941,821, 6,833,540, and 6,846,288 Insofar as we are aware, however, a method utilizing this effect has not yet been implemented in a commercially–available device or in a device which has obtained FDA approval.

As will be described more particularly below, the present invention utilizes the "photoacoustic effect", together with the method, herein referred to as the Frequency–Change by Wavelength–Control (or FCWC) method described below and in the above–cited US Patent 6,621,278 and PCT Applications, for producing a glucose monitoring device capable of achieving high reliability without a need for frequent recalibration as compared to other known methods.

When the FCWC method is used in this aspect of the present invention, the energy wave transmitted through the transmission channel is the acoustic wave generated by the "photoacoustic effect"; and the medium of the channel is the body containing the target substance to be monitored, e.g. glucose in a patient's blood.

Embodiments of the present invention are described below which utilize the FCWC (Frequency–Change by Wavelength–Control) method described in the above–cited US Patent 6,621,278, to produce a precise measurement of the transit time of an acoustic wave through a transmission channel, and thereby of the concentration of the target substance being monitored to the extent that it changes this transit time by a change in the transit velocity and/or the transit distance. This aspect of the present invention utilizes the selective absorption of energy by the target substance, and particularly the "photoacoustic effect", for generating the acoustic waves used in the FCWC method. Accordingly, the present invention enables changes in glucose concentration to be measured with a high degree of accuracy, reliability and repeatability.

The invention, however, can also be implemented by using the FCWC method without the "photoacoustic effect", in order to measure the concentration of the glucose (or other target substance) according to the heat generated by the target substance, since

such generated heat also changes the transit time of an acoustic wave through an acoustic channel.

According to another aspect of the present invention, therefore, there is a provided a method of non–invasively measuring the concentration of a target substance within a body, comprising: transmitting acoustic waves through an acoustic wave transmission channel in the body to a detector at the opposite end of the acoustic wave transmission channel; applying to the body in the acoustic wave transmission channel energy highly absorbable by the target substance, as compared to other substances, to heat the portion of the body within the acoustic wave transmission channel according to the concentration of the target substance in the body; detecting the acoustic waves in the transmission channel to output an electrical signal having a frequency corresponding the frequency of the acoustic waves transmitted through the channel by the acoustic wave transmitter; controlling the acoustic wave transmitter to change the frequency thereof such that the detector detects a whole integer number of wavelengths irrespective of variations in the target substance concentration with the body; and utilizing the frequency of the detector output signal to produce a measurement of the target substance concentration. The magnitude of the detector output signal may also be used in producing the measurement of the target substance concentration.

An advantage of this aspect of the present invention is that it enables the FCWC method to be used in two independent manners for measuring the concentration of the target substance. Thus, it uses the selective heating by the target substance to produce, by the “photoacoustic effect”, the acoustic waves used in the FCWC method. It also enables the increase in temperature produced by the selective heating to be precisely measured by the FCWC method to provide a measurement of the glucose concentration. In both cases, the FCWC method enables precisely measuring the change in transit time of the acoustic wave, and thereby any condition such as the change in temperature and/or composition, affecting the transit velocity of the acoustic wave. Thus, both techniques can be used in any particular monitoring operation, in order to improve the accuracy and reliability of the final result by executing one technique to extract data from the monitored site useful to determine concentration by the other techniques, or to corroborate the results produced by the other technique.

The present invention also enables a number of acoustic channels to be established through the monitored region for extracting therefrom various types of information which can be used to reduce the extraneous influences, and thereby to provide a more accurate measurement of the concentration of the target substance within the body.

According to another aspect of the present invention, therefore, there is provided a method of non–invasively measuring the concentration, or change in concentration, of a target substance within a body, comprising: transmitting acoustic waves through at least two separate acoustic channels in the body; applying to one of the channels energy which is selectively absorbable by the target substance to thereby heat the respective channel according to the concentration of the target substance therein; and measuring the difference in temperature between that in the one channel with respect to that in the other channel, to thereby provide a measure of the concentration, or change in concentration, of the target substance in the body.

According to still further aspects, the invention also provides apparatus for monitoring a condition, particularly for non–invasively measuring the concentration, or change in the concentration, of a target substance within a body according to the above methods.

In the described preferred embodiments, the pulse source is a laser having a wavelength selectively absorbable by the target substance; and the target substance is a constituent of the blood of a person, particularly the glucose in the person's blood. It will be appreciated, however, that the invention can use other pulse sources and can be used for determining the concentration, or change in concentration, of other target substances within other bodies.

Further features and advantages of the invention will be apparent from the description below.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

Fig. 1 is a block diagram illustrating one form of system constructed in accordance with the above–cited U.S. Patent 6,621,278 for precisely monitoring various

conditions having a known relation to, or influence on, the transit times of energy waves through a transmission channel;

Fig. 2 is a block diagram illustrating the system of Fig. 1 but modified to receive the cyclically–repeating energy wave directly, rather than the echoes thereof;

Fig. 3 is a block diagram illustrating the system of Fig. 1 applied with respect to an amplitude–modulated electromagnetic carrier wave in accordance with the present invention;

Figs. 4a–4d illustrate a series of waveforms helpful in understanding the operation of the system of Fig. 3;

Fig. 5 is a diagram illustrating how the modulation frequency (MHz) varies with the distance (m) in the system of Fig. 3;

Fig. 6 is a diagram illustrating a measuring system constructed in accordance with one aspect of the present invention utilizing a phase–locked loop circuit for continuously changing the frequency of the transmitter according to changes in the monitored condition; and

Figs. 7–12 are diagrams illustrating the invention implemented in various methods for monitoring blood glucose levels in a non–invasive manner.

THE BASIC FCWC METHOD

Fig. 1 is a block diagram illustrating the basic FCWC (Frequency–Change by Wavelength–Control) measuring method of the above–cited US Patent 6,621,278 and PCT Applications. The illustrated system is an echo system in which the distance to target T is measured by measuring the transit time taken by a cyclically–repeating energy wave transmitted at point A towards the target T until its echo is received at point B. The distance ATB thus constitutes the transmission channel between locations A and B.

The system illustrated in Fig. 1 thus includes a transmitter 2 at location A for transmitting the cyclically–repeating energy wave towards target T, and a receiver 3 at location B for receiving the echo of the cyclically–repeating energy wave after reflection from target T. Initially, the energy wave is continuously transmitted from an oscillator 4 under the control of a switch 5 until the echoes are received by receiver 3; once the echoes are received, switch 5 is opened so that the received echo signals are then used for

controlling the frequency of transmission of the cyclically–repeating energy wave by transmitter 2.

As shown in Fig. 1, the signals received by receiver 3 are fed to a comparator 6 via its input 6a. Comparator 6 includes a second input 6b connected to a predetermined bias so as to detect a predetermined fiducial or reference point in the received signal. In the example illustrated in Fig. 1, this predetermined fiducial point is the "zero" cross–over point of the received signal, and therefore input 6b is at a zero–bias. Other reference points could be used as the fiducial point, such as the maximum or minimum peak of the received signals.

The output of comparator 6 is fed to an amplifier or monostable oscillator 7 which is triggered to produce an output wave or signal for each fiducial point (zero cross–over point) in the signals received by the receiver 3. The signals from amplifier 7 are fed via an OR–gate 8 to the transmitter 2. OR–gate 8 also receives the output from oscillator 4 when switch 5 is closed.

Switch 5 is opened when the transmitter 2 receives a continuous stream of signals from amplifier 7 via OR–gate 8. When switch 5 is opened, transmitter 2 will thus transmit at a frequency determined by the fiducial points in the reflected signals received by receiver 3 and detected by comparator 6 to control amplifier 7. Accordingly the frequency of transmission by transmitter 2 will be such that the number of waves of the cyclically–repeating energy wave transmitted from location A and received in location B, i.e., in the loop including the transmission channel ATB, will be a whole integer.

It will thus be seen that while the frequency of the transmitter 2 will change with a change in the distance to the target point T, the number of wavelengths (λ) in the signal transmitted through the loop including the transmission channel ATB, from the transmitter 2 to the target T and reflected back to the receiver 3, will remain a whole integer. This is because the transmitter 2 transmissions are controlled by the fiducial points (zero cross–over points) of the signals received by receiver 3. This change in frequency by the transmitter 2, while maintaining the number of waves in the loop of the transmission channel ATB as a whole integer, enables a precise determination to be made of the distance ATB, and thereby of the distance to the target point T. Thus, as known:

$$F = C/\lambda$$

Where: F and C are the frequency and velocity, respectively, of the cyclically–repeating energy wave in the respective medium; and λ_L is the wavelength. For example, if the energy wave is an acoustic wave, and the medium is air under normal temperatures and pressures, C=340,000 mm/sec. Accordingly, if F=34 KHz, then λ–10mm.

Assuming the initial transmit path of transmission channel ATB (Fig. 1) is 100 mm, it will be seen that the number of wavelengths in the loop of this channel will be 10.

Now assuming that the transit distance of transmission channel ATB is increased by 1 mm, i.e., from 100 mm to 101 mm. While this transit distance is now increased from 100 mm to 101 mm, the transit time will also be increased. However, since the frequency of transmitter 2 is controlled by the fiducial point of the signals received by receiver 3, the transmitter 2 will still produce the same number of waves during this increased transit time, and therefore the waves will be slightly increased in length. Thus, the increased wavelength will be 101/10=10.1 mm. The frequency of transmitter 2 will therefore be changed from 34 KHz to 340,000/10.1=33,663 KHz.

The frequency will thus be decreased by 337 Hz when the distance is increased by 1 mm. Such a frequency change can be easily measured. If the distance is changed by 0.001 mm (rather than 1 mm), the frequency change will be 0.337 Hz, which would be extremely difficult, if possible at all, to measure in a practical manner. However, such a small frequency change can be easily measured in the system illustrated in Fig. 1 by including a summing circuit which continuously sums the measured frequency changes over a predetermined time, e.g., 100, 1,000, 10,000, or more cycles, and produces periodic read outs of the summed changes.

Thus, the zero cross–over points detected in comparator 6, which are used for controlling the frequency of the transmitter 2, are also fed to a counter 10 to be counted "N" times, and the output is fed to another counter 11 controlled by a clock 12. Counter 11 produces an output to a microprocessor 13 which performs the computations according to the parameter to be detected or measured, and a display 14 which displays the output of the microprocessor.

It will thus be seen that the system illustrated in Fig. 1 may be used for precisely measuring not only distance, but any other parameter having a known relation to the transit time of movement of the energy wave through the medium. It will also be seen

that the medium could be a liquid, a solid, or a gas; and that the energy wave could be an electromagnetic wave, an acoustic wave, etc. Since the measurement is done digitally, it is not subject to the limitations of accuracy, sensitivity and repeatability characteristic of analogue measurements. The measurement may be changes in the parameter during the measurement period, or the absolute value of the parameter at any instant during the measurement period.

Fig. 2 illustrates a modification in the system of Fig. 1, wherein the acoustic transmitter 22 transmits directly to the receiver 23, rather than by reflection, so that the transit distance of the transmission channel, and therefore the parameter measured by the control and measuring system 24, will be the actual line–of–sight distance between the transmitter and receiver.

Fig. 3 is a block diagram illustrating the invention implemented with respect to a method and apparatus utilizing an amplitude–modulated electromagnetic carrier waves, e.g., for measuring distance from an object. Such a system using very high carrier frequencies enables the use of compact, narrow, beam antennas or optical systems for transmission and reception.

Thus, in the system of Fig. 3, the transmitter includes a generator 70 for generating a cyclically–repeating electromagnetic carrier wave, and a modulator 71 for amplitude–modulating the carrier wave by a cyclically–repeating electromagnetic modulating wave. The modulated carrier wave is transmitted by the transmitter 72 towards the object 73 whose distance is being measured.

The modulated carrier wave, after being reflected by the object 73, is received by a receiver 74 and demodulated by a demodulator 75 separating the modulating wave from the received wave. In the illustrated system, there is further included a delay device 76, such as an acoustic delay line, for producing a phase shift of up to 360° in the separated modulating signal, before that signal is processed by the processor 77, in the manner described above, for detecting fiducial point of the received modulating signal and utilizing it for changing the frequency of the modulator 71 such that the number of modulating waves in the loop of the transmission channel is a whole integer.

Thus, the system illustrated in Fig. 3 provides feedback of the modulation frequency. The value of the modulation frequency will be set automatically so as to produce a phase shift in the feed–back loop of up to 360°. Thus:

$$fm = \frac{P}{\frac{2d}{c} + \frac{L}{v_S}}$$

where: *fm* – modulation frequency,
p – integer number,
d – distance to obstacle,
c – light velocity,
L – length of delay line,
V_S – sound velocity in delay line.

The provision of the acoustic delay line 76, which is optional, adds an artificial distance to the measurement, e.g., when a relatively high frequency is used and thereby a relatively small wave length is involved, or when otherwise there is a relatively short transit distance between the transmitter and the receiver.

It will be appreciated that the carrier wave generator 70, and also the modulator 71, could operate at the radio frequency, infrared, or optical bands of the electromagnetic spectrum. For example, the generator 70 could be in the GHz range, and the modulator 71 could be in the MHz range. The delay line 76 could be an acoustic delay line. In this example, if the integer number (p) is equal to 5, the length of the delay line (L) would be 5 mm, and the sound velocity in the delay line (v_S) would be 5,000 m/sec.

Fig. 4a illustrates the modulated carrier wave transmitted by transmitter 72, after having been amplitude–modulated by the signal from modulator 71 (point A), and Fig. 4b illustrates the modulated carrier wave outputted (point B) from the receiver 74, wherein it will be seen that the received wave has been phase shifted because of the change in distance of the object from the transmitter and receiver. Fig. 4c illustrates the demodulated wave (point C); and Fig. 4d illustrates the de–modulated wave (point D) after having been phase shifted by the delay line 76.

Fig. 4c also illustrates three examples of the predetermined fiducial point in the received signal, namely the "zero" cross–over point indicated by line a —— a, the maximum peak indicated by line b —— b; and minimum peak indicated by line c —— c, which may be used to change the frequency of the modulated wave such that the number of received de–modulated waves will be a whole integer.

Fig. 5 illustrates an example of the manner in which the modulation frequency (MHz) varies with the distance (m).

THE PHASE–LOCKED LOOP

Fig. 6 illustrates a system similar to that of Fig. 1, but based on a phase–locked loop for continuously changing the frequency of the transmitter according to changes in the monitored condition while maintaining the number of waves in the transmission channel loop as a whole integer.

In Fig. 6, the transmission channel is generally designated 100. It includes a transmitter 101 at one end, and a receiver 102 at the opposite end. The illustrated system further includes a phase–locked loop (PLL) 103 having an input 103a from the receiver 102 and an output 103b to the transmitter 101 of the transmission channel 100. Thus, PLL 103 includes a VCO (voltage–controlled oscillator) 104 which drives transmitter 101 of the transmission channel 100, and a phase detector 105 having one input from VCO 104, and a second input from receiver 102 of the transmission channel 100. Phase detector 105 thus produces an output corresponding to the difference in phases between the two inputs. The output of phase detector 105, after passing through a low–pass filter 106, is used to control the VCO 104 which drives transmitter such that the number of waves in the loop of the transmission channel 100 is and remains a whole integer.

As described above, the cyclically–repeating energy wave in transmission channel 100 may be an EMF wave, a sonic wave, or a modulated carrier wave; the transmission channel itself may be a gas, liquid or solid; and the monitored condition may influence the transit velocity and/or the transit distance of the cyclically–repeating energy wave through the transmission channel. Thus, any one of those conditions will influence the transit time of the energy wave through the transmission channel. The phase difference detected by phase detector 105 will correspond to the change in the transit time of the

energy wave through the transmission channel 100, and thereby to the changes in the monitored condition which influence this transit time.

The phase shift measured by phase detector 104 can be computed as follows:

$$\Delta\Theta = 2\pi\frac{L}{\lambda} = 2\pi\frac{L\cdot f}{c} = 2\pi\cdot t\cdot f\,[rad]$$

where: Θ – phase shift, rad,

L – distance between Transmitter and Receiver, m,

λ – length of energy wave in Medium, m,

f – frequency of VCO Hz,

c – velocity of energy propagation in Medium, m/sec,

t – transit time in medium, sec.

This phase shift appears as a voltage U on the output of the low–pass filter 104, as follows:

$$U = K_{PD}\cdot\Delta\Theta$$

where K_{PD} – transform function coefficient of the phase detector.

The frequency of VCO 104 is controlled by the output voltage U applied as a negative feed back to the VCO, as follows:

$$f = f_0(1 - K_{VCO}\cdot U)$$

where K_{VCO} – transform function coefficient of VCO.

Thus, an increase in the transit time results in a decrease of VCO frequency, and vice versa. Combining all equations

$$f = \frac{f_0}{1 + K_{PD} \cdot K_{VCO} \cdot 2\pi \cdot f_0 \cdot t}$$

It will be seen that the frequency of VCO 104 varies with, and is stabilized on, a value that depends on the transit time of the energy wave through the transmission channel 100. Since this transit time varies in a known manner with the condition being monitored, as noted above, the output of VCO 104 provides an indication of the monitored condition. The output of VCO 104 may therefore be displayed in a display device 107, and may also be stored, further processed, and/or used for controlling operation of another device, e.g., an alarm, etc.

NON–INVASIVE GLUCOSE MONITORING (FIGS. 7–12)

The apparatus illustrated in Fig. 7 includes a measuring circuit as described above with respect to Figs. 1–6 for non–invasively monitoring changes in the concentration of a target substance TS in the blood flowing through a monitored site 202 of a person. As indicated earlier, the method described is particularly useful for monitoring changes in the concentration of glucose in blood. Therefore the target substance TS is hereinafter referred to as glucose, but it will be appreciated that the invention could also be used for monitoring other target substances in other bodies, such as other constituents of blood, or constituents of urine, constituents of other biological fluids or other types of fluids, e.g., industrial fluids, or constituents of other bodies, i.e., solids and gases as well as liquids.

The apparatus illustrated in Fig. 7 includes a laser 203 which applies laser pulses via an optical fiber 204 to a selected region of the monitored site 202. Laser 203 may include a single laser, or a combination of lasers, having a wavelength or combination of wavelengths selectively absorbable by the glucose TS within the blood flowing through monitored site 202, as compared to other substances in the region exposed to the laser energy. As a result, the absorption of the laser energy by the glucose is effective to heat the respective region according to the glucose concentration in the blood. This absorption of the laser energy by the glucose generates, by the "photoacoustic effect", a series of acoustic waves, shown at 205 in Fig. 7, which are propagated through an acoustic channel 206 at a frequency corresponding to that at which the laser is pulsed. The acoustic waves so generated in channel 206 by the glucose TS are detected by an